

EUROPEAN PATENT APPLICATION

Application number: 85305780.0

Int. Cl.: **C 07 D 223/16**  
**//C07C87/28**

Date of filing: 14.08.85

Priority: 05.09.84 US 647552

Date of publication of application:  
 12.03.86 Bulletin 86/11

Designated Contracting States:  
 AT BE CH DE FR GB IT LI LU NL SE

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Method for preparing 6-chloro-N-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

A novel process for preparing 6-chloro-N-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine comprising cyclizing N-methyl-N-[2-(2'-chlorophenyl) ethyl]-2-chloroethylamine hydrochloride in a solution of trichlorobenzene and aluminum chloride.

1        METHOD FOR PREPARING 6-CHLORO-N-METHYL-  
         2,3,4,5-TETRAHYDRO-1H-3-BENZAZEPINE

         This invention relates to a novel process for pre-  
5        paring 6-chloro-N-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine.  
         This compound has been disclosed as having utility as an  
         alpha<sub>2</sub> antagonist, a pharmacological action which is  
         associated with a broad spectrum of beneficial cardiovascular  
         activity. The compound is particularly useful as an anti-  
10        hypertensive agent. (United States Patent No. 4,465,677)

BACKGROUND OF THE INVENTION

         In the above noted patent the title compound is  
15        prepared by cyclizing N-methyl-N-[2-(2'-chlorophenyl)-  
         ethyl]-2-chloroethylamine hydrochloride under Friedel-Crafts  
         conditions. The cyclization step is carried out using Lewis  
         acids such as aluminum chloride in a melt of ammonium chloride.  
         United States Patents 4,251,660 and 4,200,754  
20        disclose a method of preparing tetrahydroisoquinolines. Both  
         of these patents employ aluminum chloride as the cyclization  
         agent. The '660 patent teaches that the reaction is done in  
         the absence of an organic solvent. The '754 patent discloses  
         that the reaction is done with conventional Friedel Crafts  
25        solvents, i.e., methylene chloride, tetrachloroethylene or  
         dichloroethane. Other well known solvents employed during the  
         Friedel Crafts reaction are nitrobenzene or decalin.

         The above methods which employ either the con-  
         ventional solvents or a melt in the process all proved  
30        commercially unsatisfactory when used in an attempt to prepare  
         6-chloro-N-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine. These  
         prior art methods resulted in very poor yields, from  
         relatively no yield to about 25%, with the production of  
         undesired isomers and other impurities.

35        In addition to the above conventional Friedel-Crafts  
         solvents, chlorinated organic solvents such as monochloro and



- 1 conditions such as temperature, pressure, and concentration of  
aluminum chloride. The application of pressure permits a  
higher concentration of aluminum chloride thereby decreasing  
reaction time considerably, more than four fold.
- 5 Advantageously, the pressure is greater than two atmospheres.  
The free base obtained from the hydrochloride salt after  
treatment with aqueous alkali is purified by distillation  
followed by conversion to the hydrochloride and recrystal-  
lization from methanol-ethyl acetate.
- 10 The reaction mixture is conveniently and optionally  
worked up by methods known to the art. Most commonly this  
involves quenching the reaction mixture, removal of the  
aluminum salts followed by extraction and purification of the  
final product.
- 15 The method of this invention is successfully carried  
out employing the isomers of trichlorobenzene, for example, the  
reaction progresses as expected if the 1,2,4; 1,2,3; or 1,3,5  
isomer of trichlorobenzene or mixtures of them is used as the  
solvent. Advantageously, technical grade 1,2,4 isomer is  
20 employed because it has the lowest melting point (17° C.) and  
thus the greatest liquid working range.
- The cyclization agent is aluminum chloride which forms  
a Friedel-Crafts complex which in turn cyclizes to form the  
desired product. Stoichiometric quantities of aluminum  
25 chloride may be used. In practice from about 2.4 to 3 mole  
equivalents of aluminum chloride compared to the starting  
material (Formula I) are employed. Excess amounts of aluminum  
chloride are not detrimental to the reaction.
- The following example illustrates the process of this  
30 invention but is not to be construed as a limitation thereof.

#### EXAMPLE

- A mixture of 121 l of 1,2,4-trichlorobenzene and 19.5  
Kg. (75.0 m) of N-methyl-N-[2-(2'-chlorophenyl)ethyl]-2-hydroxy-  
35 ethylamine was agitated at a temperature of 20-30° C. and a  
homogenous solution was obtained. Phosphorous pentachloride,  
7.2 Kg. (34.6 m) was added and the temperature was brought to

1 110° C.

To the above solution, containing N-methyl-N-[2-(2'-chlorophenyl)ethyl]-2-chloroethylamine hydrochloride, was slowly added 24.4 Kg. (18.3 m) of aluminum chloride while the temperature was maintained between 95° and 110° C. The reaction was then brought to a reflux temperature of 205° C. for six hours.

The reaction was quenched over a 2 hour period by cooling to 80° C. with an acidic aqueous mixture (450 l of H<sub>2</sub>O, 18 l of HCl) with agitation. The quench was allowed to settle and the trichlorobenzene layer was separated.

The aqueous quench was layered with toluene (120 l) and the two phase mixture was brought to a pH of at least 11 with 50% aqueous sodium hydroxide.

15 The aqueous phase was extracted with toluene (120 ml) and the phases separated. The aqueous wash was discarded and the toluene phase was fractionally distilled. After removal of the toluene, the distillate at 134° to 143° C. pot temperature and 126° to 140° C. vapor temperature at 15 to 20 torr was collected and resulted in a 91% yield of 6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine as the free base.

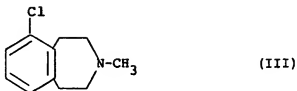
The above oily base in toluene was treated with anhydrous hydrogen chloride, then recrystallized from methanol/ethyl acetate yielded 6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, m.p. 268-270° C (d).

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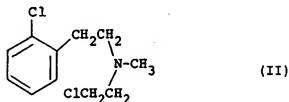
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Claims.

1. A process for the preparation of a compound of the formula (III)



which comprises cyclisation of a compound of formula (II)



in the presence of aluminium trichloride, characterised in that the solvent comprises trichlorobenzene.

2. A process as claimed in claim 1 in which the solvent is 1,2,4-trichlorobenzene.

3. A process as claimed in claim 1 or claim 2 in which the reaction is carried out at a temperature of from about 180°C to about 215°C for a period of from about 3 to 8 hours.

4. A process as claimed in any one of claims 1 to 3 in which the compound of formula (II) is prepared by reaction of a compound of formula (I)

